IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Kei Roger Aoki, et al.	Examiner: Anish Gupta
Serial No.: 10/726,904	Group Art Unit: 1654
Filed: December 2, 2003	Confirmation No.: 4172
For: USE OF THE NEUROTOXIC COMPONENT OF A BOTULINUM TOXIN FOR TREATING A SPASTIC MUSCLE	

Mail Stop - Appeal Brief
Commissioner for Patents
P.O. Box 1450
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BRIEF ON APPEAL

(1) Real Party in Interest

The real party in interest is Allergan, Inc.

(2) Related Appeals and Interferences

There are related appeals pending for U.S. Application Serial No. 10/460,898, appeal filed June 10, 2008, U.S. Application Serial No. 10/461,829, appeal filed June 27, 2008, and U.S. Application Serial No. 10/933,723, appeal filed July 2, 2008.

(3) Status of Claims

Claims 1-2, 4-5, 29, 47 and 63 are pending and stand finally rejected.

Claims 6-28 have been cancelled in a Response dated September 26, 2006.

Claim 3 has been cancelled in a Response dated April 12, 2007.

Claims 30, 46, and 62 have been cancelled in an Interview Summary and Response dated June 4, 2007.

Claims 31-45, 48-61, and 64-77 have been cancelled in a Response dated September 25, 2007.

Applicants appeal the rejections of claims 1-2, 4-5, 29, 47 and 63.

(4) Status of Amendments

All claim amendments were entered prior to the final Office Action, and no claim amendments are pending.

(5) Summary of Claimed Subject Matter

Three independent claims are involved in this appeal, claims 1, 5, and 29.

The invention of independent claim 1 is a method for treating strabismus in a patient by administering a therapeutically effective amount of the neurotoxic component of a botulinum toxin to the patient to thereby treat the patient's strabismus. The neurotoxic component has a molecular weight of about 150 kilodaltons. See, e.g., specification at page 3, lines 8-28; page 5, lines 25-36; page 7, line 6 to page 8 line 38; page 9, line 9 to page 10, line 11; pages 23-24, Example 13; and page 26, original claims 1-5.

Independent claim 5 recites a method for treating strabismus in a patient. The method comprises administering a therapeutically effective amount of the neurotoxic component of only a botulinum toxin type A to the patient to thereby treat the patient's strabismus. The neurotoxic component has a molecular weight of about 150 kilodaltons. See, e.g., specification at page 3, lines 8-28; page 5, lines 25-36; page 7, line 6 to page 8 line 38; page 9, line 9 to page 10, line 11; pages 23-24, Example 13; and page 26, original claims 1-5.

Independent claim 29 recites a method for treating strabismus in a patient. The method comprises administering a therapeutically effective amount of the neurotoxic component from a single botulinum toxin type selected from the group consisting of botulinum toxin types A, B, C, D, E, F and G to the patient to thereby treat the patient's strabismus. The neurotoxic component has a molecular weight of about 150 kilodaltons. See, e.g., specification at page 3, lines 8-28; page 5, lines 25-36; page 7, line 6 to page 8 line 38; page 9, line 9 to page 10, line 11; pages 23-24, Example 13; and page 26, original claims 1-5.

(6) Grounds of Rejection to be Reviewed on Appeal

Rejection 1: Priority under 35 U.S.C. § 119 to parent applications U.S. Serial Nos. 08/173,996 and 08/627,118 has been denied, as the parent applications allegedly do not enable the claims under 35 U.S.C. § 112, first paragraph.

Rejection 2: Claims 1, 2, 4, 5, 29, 47, and 63 stand rejected under 35 U.S.C. § 103 as patentably obvious in view of Balkan *et al.* (*Annals of Ophthalmology* 1991; 23(9): 326-333) or Han et al. (*Journal of Pediatric Ophthalmology and Strabismus*, 2001; 38(2): 68-71) in view of Kohl *et al.* (*Movement Disord.* 2000; 15(Suppl 3): 165), Tse *et al.* (*Eur. J. Biochem.* 1982; 122(3): 493-500), and Aoki *et al.* (U.S. Patent No. 6,113,915).

Rejection 3: Claims 1, 2, 4, 5, 29, 47, and 63 stand rejected under 35 U.S.C. § 103 as patentably obvious in view of Balkan *et al.* (*Annals of Ophthalmology* 1991; 23(9): 326-333) or Han *et al.* (*Journal of Pediatric Ophthalmology and Strabismus*, 2001; 38(2): 68-71) in view of Kohl *et al.* (*Movement Disord.* 2000; 15(Suppl 3): 165), Aoki *et al.* (U.S. Patent No. 6,113,915), and Aoki *et al.* (U.S. Publication No. 2001/0018415).

(7) Argument

Rejection 1: Whether parent application U.S. Serial No. 08/173,996 enables claims 1, 2, 4, 5, 29, 47, and 63 such that priority to the '996 application under 35 U.S.C. § 119 should be granted.

A. Grouping of Claims for Rejection 1

Claims 1, 2, 4, 5, 29, 47, and 63 stand or fall together.

B. Arguments for Reversal of Examiner's Rejection 1

As a preliminary matter, Applicants believe that the Examiner intended to deny priority under 35 U.S.C. § 120, because only priority claims to U.S. utility applications (section 120) have been made by Applicants, and no priority claims to foreign or U.S. provisional applications (section 119) have been made.

Prior responses and evidence submitted by Applicants overcame a written description rejection by the Examiner under 35 U.S.C. § 112, first paragraph. Office Action of November 29, 2007 at page 5. Additionally, the Examiner has acknowledged that the claims are enabled with respect to "how to make" the claimed invention, but contends that the claims are not enabled for 'how to use' the neurotoxic component in a clinical setting". Office Action of November 29, 2007 at pages 7-8. "The question was not whether one could make or isolate the purified toxin but whether one could use it in a clinical setting." Office Action of April 7, 2008 at page 7. Thus, the narrow issue in this rejection is alleged lack of enablement under 35 U.S.C. § 112, first paragraph for "how to use" the claimed invention.

The Examiner contends that the specification of parent application U.S. Serial No. 08/173,996 (hereinafter, "the '996 application"), filed December 28, 1993, does not provide enablement under 35 U.S.C. § 112, first paragraph for "how to use" the currently pending claims. The Examiner alleges that the '996 application does not disclose methods that one of ordinary skill in the art could utilize to render the neurotoxic component clinically effective, and given the state of the art as recited by Schantz *et al.* (*Microbiol. Rev.* 1992; 56(1): 80-99; Evidence Exhibit A) one of ordinary skill would have required undue experimentation to practice the claimed invention. For example, the Examiner stated that "[t]he issue here is whether the art, as of the filing date of '996, provided ample guidance on how to make purified botulinum toxin useful in a clinical setting (treatments)." Office Action of April 7, 2008 at page 7.

The test for enablement is whether one skilled in the art at the time Applicants filed the present application could make and use the claimed invention from the disclosures in the specification coupled with the information known in the art without "undue" experimentation. In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991). Factual considerations that can be weighed when determining whether "undue" experimentation would be required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the relative skill of those in the art, (5) the predictability or unpredictability of the art, (6) the amount of direction or guidance provided, (7) the presence or absence of working examples, and (8) the quantity of experimentation

necessary. See, In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Any part of the specification can support an enabling disclosure, including a background section that discusses or even disparages the subject matter disclosed therein. Callicrate v. Wadsworth Mfg., Inc., 427 F.3d 1361, 1374 (Fed. Cir. 2005). All the evidence must be considered, and any conclusion of nonenablement must be based on the evidence as a whole. Wands 858 F.2d at 740, 8 USPQ2d at 1407.

A patent application specification is presumed to be enabled, and it is the burden of the Examiner to present evidence to rebut this presumption. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

The evidence as a whole shows that the '996 specification clearly enables one of ordinary skill to use the neurotoxic component in a clinical setting. However, the Examiner has applied the wrong standard under the law; has failed to consider all of the relevant evidence in making the rejection; and has confused obviousness with enablement. Each of these points is discussed below.

1. The evidence as a whole shows the '996 specification enables one of ordinary skill to make and use the claimed subject matter.

A consideration of the Wands factors set forth above indicates that '996 specification would have enabled one of ordinary skill to make and use the claimed subject matter:

Breadth of the claims and nature of the invention

The pending claims are directed to a method for treating strabismus using the neurotoxic component of a botulinum toxin. The invention, as provided in the present

application, was the realization that a clinician could use the neurotoxic component, purified and formulated as described in the art, in a clinical setting to treat strabismus. The breadth of the claims is relatively narrow because the claims are limited to treatment of strabismus using the neurotoxic component of a botulinum toxin.

State of the Prior Art

The state of the art, as acknowledged by the Examiner, was that it was known how to purify and formulate the neurotoxic component of a botulinum toxin. See, e.g., Office Action of April 7, 2008 at page 7. Thus, for example, one of ordinary skill would have known that the neurotoxic component, either single chain or dichain, was obtained by fermentation of *Clostridium botulinum* followed by chromatographic separation techniques. See, e.g., Wagman, J. *et al.*, *Arch Biochem Biophys* 1953; 45: 375-383; DasGupta, B., *et al.*, *J. Biol. Chem.* 1968 Mar 10; 243(5): 1065-1072; Schantz, E., pages 143-150 in Biomedical aspects of botulism, edited by Lewis, G., Academic Press, New York (1981); and Borodic, G. *et al.*, *Ophthalm Clinics of N. America* 1991 Sep; 4(3): 491-503. Evidence Exhibits B-E. Furthermore, one of ordinary skill in the art would have known that the neurotoxic component was available for purchase from commercial suppliers. See, e.g., the Brin Declaration at paragraph 18. Evidence Exhibit F. Once isolated, it was known in the art how to formulate the neurotoxic component. See, references cited in a review by DasGupta, B.R., pages 15-39 in Therapy with botulinum toxin, edited by Jankovic, J. *et al.*, Marcel Dekker, Inc., New York (1994). Evidence Exhibit G. The cited references include: Tse, C.K. *et al.*, *Eur. J. Biochem.* 1982 ; 122 : 493-500 ; and Lamanna, C., pages 333-335 in Botulinum and Tetanus Neurotoxins, edited by DasGupta, B., Plenum Press, New York (1993). Evidence Exhibits H and I.

Relative Skill of those in the Art and Predictability of the Art

The relative skill of those in the art was high, as the person of ordinary skill in the art can be characterized as a clinician or physician having knowledge of or experience with botulinum toxin. Predictability of the art is high, as it was known in the art that the

neurotoxic component is the biologically active component of a botulinum toxin. It was also known how to purify and formulate the neurotoxic component, as discussed above. Furthermore, it was known how to store the formulated neurotoxic component. See, references cited in DasGupta, supra. Evidence Exhibits H and I.

Guidance Provided and Presence of Working Examples

The '996 application discloses at page 4, lines 9-12 that a botulinum toxin can be purified (e.g., to obtain the neurotoxic component) and then stabilized and preserved (see, e.g., page 7, lines 21-28). The '966 application discloses the different components of a botulinum toxin and clearly indicates that one can use both the single and dichain forms of the neurotoxic component. See, e.g., page 3, lines 23-25. The '996 application also discloses how to administer the neurotoxic component to a patient. See, e.g., page 7, lines 11-17; page 8, lines 12-16; and page 9, line 25 to page 10, line 13. Furthermore, the '996 application describes many examples of administration of a botulinum toxin, as discussed above. In particular, the '996 application indicates how a clinician would inject toxin in the treatment of strabismus at page 9, line 21 to page 10, line 6.

The skilled clinician would be experienced with preparing and injecting pharmaceuticals as well as determining proper dosage based on the particular requirements of each patient and the severity of the condition presented. One of ordinary skill in the art would be skilled in determining proper dosage based on the particular circumstances of a patient as well as being skilled in injections involving the eye in treatment of strabismus, as indicated in the Declaration under 37 CFR § 1.132 from Dr. Leonard Smith, a recognized expert in the clinical use of botulinum toxins. Evidence Exhibit J. Dr. Smith declared, based on the '996 application, that the skilled clinician could administer to patients a therapeutically effective neurotoxic component formulation. See Smith Declaration at paragraphs 17 and 18.

In view of the above, the weight of all the evidence is that one of ordinary skill in the art would have been able to use the claimed invention in a clinical setting (i.e. "how

to use") without undue experimentation, based on the disclosures in the '996 application and knowledge of the prior art.

2. The Examiner has applied the wrong standard under the law

Despite the evidence discussed above regarding enablement of the claims by the '996 application, the Examiner has asserted the '996 specification is not enabling, contending that "[t]he issue here is whether the art, as of the filing date of '996, provided ample guidance on how to make purified botulinum toxin useful in a clinical setting (treatments)." Office Action of April 7, 2008 at page 7.

This is clearly not the standard for evaluating enablement. First, it is not the art that must enable the claimed invention, but the specification in light of the knowledge of one of ordinary skill. Second, the specification need not provide "ample guidance" on how to use a pure toxin in a clinical setting. As the Federal Circuit has held, "[n]ot every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be." See DeGeorge v. Bernier, 768 F.2d 1318 (Fed. Cir. 1985) and cases cited therein. The specification need not "necessarily describe how to make and use every possible variant of the claimed invention, for the artisan's knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, depending upon the predictability of the art." AK Steel Corp. v Sollac 344 F.3d 1234, 1244 (Fed. Cir. 2003). Indeed, "[n]othing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." In re Wright, 999 F.2d 1557 (Fed. Cir. 1993). That is, the Examiner has applied an exceedingly strict standard that is improper under the law. For this reason alone, the Board is requested to reverse the rejection for lack of enablement.

3. The Examiner has failed to consider all of the relevant evidence bearing on enablement.

Even if the proper enablement standard had been applied, the Examiner has failed to consider all of the relevant evidence bearing on enablement of the pending claims. Rather than weigh all of the evidence in evaluating enablement, the Examiner has essentially limited the evidence to be considered to a single publication, a review by Schantz *et al.* Evidence Exhibit A (hereinafter, "Schantz"). Schantz states that "[b]ecause of its lability the neurotoxin is not practical for medical applications," and "[m]ost recent information concerning the structure and pharmacology of botulinum toxin had been obtained with purified neurotoxins, but it is unlikely that these will be used in a clinical setting." Schantz, at page 82 and 89, respectively. In his reliance on Schantz, the Examiner has failed to consider the evidence as a whole, including the guidance and working examples in the '996 specification.

The Examiner has acknowledged that one of ordinary skill would have known how to make the neurotoxic component, but has pointed to statements in Schantz that "[n]o clinical trials on primates have been performed with purified neurotoxin" and "[b]ecause of its lability the neurotoxin is not practical for medical applications." Office Action at page 8 (citations omitted). The Examiner asserts Schantz teaches that "the instability of the toxin results in ineffectiveness in the clinical setting." Office Action of April 7, 2008 at page 8. In view of Schantz, the Examiner questioned "whether one could use it in a clinical setting." Office Action of April 7, 2008 at page 7.

The answer to the question posed by the Examiner is that the neurotoxic component can be formulated and stored as described, for example, in Lamanna C. *et al., Arch. Int. Pharmacodyn. Therap.* 1988; 293:69-83 (Evidence Exhibit K, hereinafter, "Lamanna") and administered in a clinical setting as described in the '996 specification. In particular, Lamanna discloses that the neurotoxic component can be dissolved in sterilized phosphate-0.2% gelatin buffer (pH 6.2-6.7) for both storage and IV injection. See, Lamanna at page 70. The '996 application states that the neurotoxic component in either its single or dichain forms is "useful in the method of the present invention." See page 3, lines 5-24. The '996 application discloses how to administer the neurotoxic

component to a patient. See page 7, lines 11-17; page 8, lines 12-16; and page 9, line 25 to page 10, line 13. The '996 application describes many examples of administration of a botulinum toxin, a generic term used throughout the specification to embrace the family of botulinum toxins, including the neurotoxic component. See page 2, lines 24-28. The Examples describe use of the neurotoxic component in a clinical setting, and thus, the '996 specification clearly provides sufficient guidance for one of ordinary skill in how to use the pure toxin in a clinical setting

The Examiner has dismissed the Declarations of Dr. Brin and Dr. Smith, stating that the Declarations are merely opinions and do not provide supporting evidence. Contrary to the Examiner's characterization, each of these Declarations provides supporting evidence upon which the Declarants base their conclusions. For example, the Declaration by Dr. Smith refers to contemporaneous publications, such as a Ph.D. thesis entitled *Characterization and stabilization of clostridium botulinum neurotoxin* by Michael C. Goodnough, published by the University of Wisconsin, March 10, 1994 (Evidence Exhibit L) and a review article by DasGupta (Evidence Exhibit G). The Goodnough thesis describes a formulation of the neurotoxic component suitable for medical use using the same lyophilization (freeze drying) process used for preparing a botulinum toxin complex. DasGupta rebuts Schantz's opinion of the stability of the neurotoxic component:

> The rationale for clinical use of the impure type A NT ["neurotoxin"] (about 80% of protein in the crystallized complex is nonneurotoxic protein) is that the nonneurotoxic proteins 'bound to the neurotoxin apparently play an important role in maintaining the toxic shape of the neurotoxin' [quoting from Schantz 1992]...'an important point regarding the use of purified neurotoxin [i.e. the neurotoxic component] besides its instability is the fact that it cannot be prepared with constant composition and activity' [quoting from Schantz E. *et al.*, *Use of crystalline type botulinum toxin in medical research*, pages 143-150 of Lewis G.E. ed., Biomedical aspects of botulism, Academic Pres, New York (1981)]. This is not true, and this prevailing view needs rectification. (emphasis added.)

The Examiner has seized upon the fact that both the Goodnough and DasGupta publications are dated after the filing date of the '996 application and discounted the

Smith Declaration on that basis. However, the Examiner has ignored the law, which clearly indicates that post-filing date publications are relevant if they provide evidence of the level of skill in the art at the time the application was filed. Gould v. Quigg, 822 F.2d 1074, 1077, 3 USPQ2d, 1304 (Fed. Cir. 1987). Here, both the Goodnough and DasGupta publications do just that. Although the Goodnough thesis was published after the filing date of the '996 application, it is reasonable to presume that the experiments reported therein were conducted before or contemporaneously with the '996 filing date. Similarly, although the DasGupta review was published after the '996 filing date, the review cites references published before the '996 filing date to support its conclusions.

Finally, the Smith Declaration refers not only to the Goodnough thesis and the DasGupta review, but also to the two Lamanna articles mentioned above. Evidence Exhibits K and I. Both of these articles were published before the filing date of the '996 application and fully support the conclusions of Dr. Smith. Thus, the Board is requested to give appropriate weight to the Declarations of Dr. Brin and Dr. Smith, recognized experts in the clinical use of botulinum toxins.

Finally, it appears from the statements in the Office Action of April 7, 2008 that the Examiner believes there is some unusual feature in the formulation and storage of the neurotoxic component that is critical to its use in a clinical setting. This is not the case. It was the present inventors who recognized that the neurotoxic component could be used in a clinical setting when formulated and stored as described in the art. When one considers the evidence as a whole and does not limit the enablement inquiry to Schantz alone, it becomes apparent that the '996 application does enable one of ordinary skill to make and use the presently claimed invention.

4. The Examiner has confused obviousness and enablement.

The Examiner believes that it is contradictory for Applicants to argue that "Schantz is wrong" with respect to enablement but "is correct" when used as evidence to support non-obviousness. Office Action of April 7, 2008 at page 10. The Examiner has misunderstood Applicants' statements and has confused obviousness with enablement.

First, the Examiner correctly quoted a statement by Applicants, in the Office Actions of December 15, 2006 page 4 and November 29, 2007 at page 4. However, the Examiner has modified and incorrectly quoted this statement in the present Office Action. For example, in the Office Action of April 7, 2008 at page 9, the Examiner incorrectly quoted Applicants as stating that "**[a]t the time of the filing of the present application, one of ordinary skill would not consider using only the purified botulinum toxin component of the botulinum toxin in clinical settings.** For example, in 1992, Schantz et al. (hereinafter the "Schantz reference") clearly stated that purified botulinum toxin is so labile that it would not be used in clinical settings..." (emphasis in original). Applicants actually stated, in response to a rejection of the claims under 35 U.S.C. § 103(a), that "[a]t the time of the filing of the present application, one of ordinary skill would not consider the teachings of the Tse reference regarding the use of pure botulinum toxin to be relevant to clinical treatment, such as the treatment of strabismus in humans. For example, in 1992, Schantz et al. [ ] clearly stated that pure botulinum toxin is so labile that it would not be used in clinical settings." See, Response of September 26, 2006 at page 9. Applicants did NOT state that one of ordinary skill would not consider using the neurotoxic component. Applicants did NOT state that the specification does not enable one of ordinary skill to use the neurotoxic component. Instead, Applicants argued, in response to an obviousness rejection, that one of ordinary skill would not consider the Tse reference to be relevant to clinical treatment. Finally, Applicants did NOT state that Schantz "is correct." Instead, Applicants argued, in response to an obviousness rejection, that the statements in Schantz teach away from the claimed invention.

Second, the Examiner has confused the standards for enablement with the standards for obviousness. In Singh v. Brake, the Federal Circuit stated that "the enablement requirement . . . looks to the objective knowledge of one of ordinary skill in the art." Singh v. Brake, 317 F.3d 1334, 1346 (Fed. Cir. 2003) (citing Spectra-Physics, Inc. v. Coherent, Inc. 827 F.2d 1524, 1532, 3 USPQ2d 1737, 1742 (Fed. Cir. 1987) (emphasis added). All the evidence must be considered, and any conclusion of nonenablement must be based on the evidence as a whole. Wands 858 F.2d at 740, 8

USPQ2d at 1407. In other words, Schantz is merely one publication to be considered among many others in the context of an objective enablement inquiry into the evidence as a whole. A review of the evidence as a whole, as discussed above, reveals that the statements put forth in Schantz are outweighed by 1) numerous other references indicating how the neurotoxic component is purified, formulated and stored, and 2) the guidance in the '996 application on how to make and use the neurotoxic component in a clinical setting.

The Federal Circuit discussed the differences between enablement and obviousness in Singh v. Brake, a case that has some similarities with the present rejection. In Singh, one of the parties to an interference argued that the Board of Patent Appeals and Interferences ("the Board") had taken internally inconsistent positions with respect to enablement of a priority application and conception of a count in the interference. The Singh court rejected the notion that the Board's positions were inconsistent. Singh 317 F.3d at 1345. With respect to obviousness and enablement, the Singh court stated that "[a]lthough the questions (1) whether or not a reference "teaches away" from a claimed invention and (2) whether or not a claimed invention provides "unexpected results" are relevant in determining whether or not a claimed invention would have been obvious, [ ] they are not the primary questions bearing on enablement." Id.

Analogous to the Board's positions in Singh, it is completely consistent for the '996 application to enable one of ordinary skill to practice the claimed methods while the statements put forth by Schantz lead one of ordinary skill away from such methods when considering non-obviousness. Analogous to the statement by the Federal Circuit in Singh, the question of whether Schantz teaches away from the present invention is not the primary question bearing on enablement. Instead, the question of whether Schantz teaches away from the present invention relates primarily to obviousness.

In view of the above, the Examiner has failed to meet his burden to show by a preponderance of evidence that the '996 application does not enable the claimed methods. Rather, an improper standard has been applied to determine enablement; the evidence as a whole has not been considered; and obviousness has been confused

with enablement. The evidence as a whole, as discussed above, shows that the '996 application would have enabled one of ordinary skill in the art to practice methods of treating strabismus with the neurotoxic component as claimed. The Board is requested to reverse the denial of priority under 35 U.S.C. § 120 to the '996 application.

Rejection 2: Whether claims 1, 2, 4, 5, 29, 47, and 63 are patentably obvious in view of Balkan *et al.* or Han *et al.* in view of Kohl *et al.*, Tse *et al.*, and Aoki *et al.*

A. Grouping of Claims for Rejection 2

Claims 1, 2, 4, 5, 29, 47, and 63 stand or fall together.

B. Arguments for Reversal of Examiner's Rejection 2

The Examiner rejected claims 1, 2, 4, 5, 29, 47, and 63 under 35 U.S.C. § 103(a) as obvious in view of Balkan *et al.* (*Annals of Ophthalmology* 1991; 23(9): 326-333) or Han et al. (*Journal of Pediatric Ophthalmology and Strabismus*, 2001; 38(2): 68-71) in view of Kohl *et al.* (*Movement Disord.* 2000; 15(Suppl 3): 165), Tse *et al.* (*Eur. J. Biochem.* 1982; 122(3): 493-500), and Aoki et al. (U.S. Patent No. 6,113,915). Exhibits M, N, O, H, and P, respectively.

Applicants have argued above that the claims are entitled to priority to the December 28, 1993 filing date of the '996 application. Given this priority date, the Han article (published 2001), the Kohl article (published in 2000), and the Aoki patent (filed in 1999) are not prior art with regard to the pending claims. The Examiner has acknowledged that the obviousness rejection will be withdrawn upon granting of the priority date as the rejection contains references which would not then be considered prior art with regard to the claims. Interview Summary of June 4, 2007 at page 3.

If, however, Applicants are not granted priority to the '996 application, Applicants assert that the claims are patentable over the combination of Balkan, Han, Kohl, Tse, and Aoki for the reasons discussed below.

The Examiner asserts that the claims are obvious because, as detailed in the Office Action of March 29, 2006, although the Balkan and Han references teach the use of complexed botulinum toxin to treat strabismus, it would have been obvious to one of

ordinary skill to use the purified neurotoxic component to treat strabismus, because, as the Examiner argues, (1) the neurotoxic component has a similar activity in the paralysis of muscles as complexed neurotoxin; (2) the neurotoxic component has a similar activity against spontaneous release of acetylcholine; and (3) because botulinum toxin complexes (having a molecular weight greater than 150 kDa) may result in slower rate of diffusion of the botulinum toxin away from a site of intramuscular injection. Office Action of March 29, 2006 at pages 3-5.

> The Examiner has the burden of presenting a *prima facie* case of obviousness.
>
> A *prima facie* case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability. (37 CFR 1.56(b)(2)).

For an invention to be obvious under § 103, the factors set forth in Graham v. John Deere Co. of Kansas City, 383 U.S. 1 (1966) must be considered, including an analysis of the scope and content of the prior art and the differences between the claimed subject matter and the prior art. Indeed, "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness" (KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727 (2007), quoting In re Kahn, 441 F.3d 997, 988 (Fed. Cir. 2006)).

There is no teaching or disclosure in the cited references, nor indeed any explicit rationale given by the Examiner, for why one of ordinary skill in the art would have modified the methods as disclosed in Anderson in view of Tse, Kohl and Aoki. A person of ordinary skill in the art would not have combined the references for at least for the following reasons.

The Balkan and Han references relate to the injection of complexed botulinum toxin into a human muscle for treating strabismus. On the other hand, the Tse reference relates to the injection of the neurotoxic component into a non-spasmodic rat

hind leg muscle. Clearly, the Balkan and Han references relate to human muscles, while the Tse reference relates to rat muscles; and it is well documented that the effects of the neurotoxic component on rat muscles cannot be extrapolated to that of humans. For example, Moyer *et al.* asserts that:

> Unfortunately, given the species-specificity of the various toxin types, rodent studies must be considered inconclusive with respect to predicting the relative clinical potency of the various types of BTX.

Moyer, E. pages 71-85 in Therapy with Botulinum Toxin, edited by Jankovic, J. *et al.*, Marcel Dekker, Inc., New York (1994). Evidence Exhibit Q. Thus, one of ordinary skill would not combine the Balkan and Han references with the Tse reference because the information reported in the latter relating to the effects of the neurotoxic component on mouse muscles cannot be applied to human muscles. At the time of filing the present application, one of ordinary skill would not have considered the teachings of the Tse reference regarding the use of the neurotoxic component to be relevant to clinical treatment of strabismus in humans.

The Kohl reference was cited for the proposition that the effects of the 140 kDa neurotoxic component on mouse muscles can be applied to human muscles. In making this argument, the Examiner relies on the fact that the 140 kDa neurotoxic component of the Tse reference is the same as the neurotoxic component of the Kohl reference. However, the Examiner has not provided any evidence that the two neurotoxins are the same. As such, Applicants' position that the data regarding the use of the 140 kDa neurotoxic component in mice cannot be extrapolated to humans remains unchallenged.

The teachings of the Balkan and Han references relate to methods for clinical treatment of strabismus in humans. On the other hand, the teachings of the Tse reference relate to improved vaccines and probes. The use of a compound as a drug for treating strabismus in humans is very different from the use of that compound as an antigen or a probe, and the practice of the two methods may be entirely incompatible with each other. For example, one of the goals in using the neurotoxic component in treating strabismus is to administer the toxin in a dose/regimen so as to not induce

antibody production against the toxin, since the induction of antibody against the toxin would render it less effective. On the other hand, the primary goal of using the neurotoxic component as an antigen is to induce antibody production against the toxin. Since the teachings of the Balkan and Han references are for a different purpose than that of the Tse reference, one of ordinary skill would not combine these references.

The Examiner alleges that one of ordinary skill would be motivated to modify the teachings of the Balkan and Han references based on the Aoki reference to use the neurotoxic component because a high rate of diffusion of the toxin is desirable for the treatment of strabismus. Office Action of March 29, 2006 at pages 4-5.

However, this assumption presumes that a physician would rely on the diffusion of the neurotoxic component to achieve better treatment. It is important to understand that highly diffusing neurotoxins would diffuse to non-targeted muscles, compromising treatments. If a physician desires the neurotoxic component to be at a certain region of a muscle, he/she would simply inject the it into that region. For example, a physician can make multiple injections of the neurotoxic component along the length of a muscle in order for the entire muscle to be affected. Thus, it appears that the Aoki reference is teaching away from the present invention, by teaching that the neurotoxic component would diffuse more quickly to adjacent muscles, and thus should not be used to treat strabismus. Indeed, it is the Applicant who surprisingly discovered that the neurotoxic component may be effectively used for treating strabismus.

In view of the above, it is apparent that there is no rational basis for believing one of ordinary skill would have combined the cited references. Thus, a *prima facie* case of obviousness has not been established. Accordingly, the Board is requested to reverse the rejection of claims 1, 2, 4, 5, 29, 47, and 63 under 35 U.S.C. § 103(a).

Rejection 3: Whether claims 1, 2, 4, 5, 29, 47, and 63 are patentably obvious in view of Balkan *et al.* or Han *et al.* in view of Kohl *et al.*, Aoki *et al.*, and Aoki *et al.*

A. Grouping of Claims for Rejection 3

Claims 1, 2, 4, 5, 29, 47, and 63 stand or fall together.

B. Arguments for Reversal of Examiner's Rejection 3

The Examiner rejected claims 1, 2, 4, 5, 29, 47, and 63 under 35 U.S.C. § 103(a) as obvious in view of Balkan *et al.* (*Annals of Ophthalmology* 1991; 23(9): 326-333) or Han *et al.* (*Journal of Pediatric Ophthalmology and Strabismus*, 2001; 38(2): 68-71) in view of Kohl *et al.* (*Movement Disord.* 2000; 15(Suppl 3): 165), Aoki *et al.* (U.S. Patent No. 6,113,915), and Aoki *et al.* (U.S. Publication No. 2001/0018415). Exhibits M, N, O, P, and R, respectively.

The Examiner asserts that the claims are obvious because, as detailed in the Office Action of March 29, 2006, although the Balkan and Han references teach the use of complexed botulinum toxin to treat strabismus, it would have been obvious to one of ordinary skill to use the purified neurotoxic component to treat strabismus, because, as the Examiner argues, (1) the neurotoxic component has a similar activity against spontaneous release of acetylcholine; and (2) because botulinum toxin complexes (having a molecular weight greater than 150 kDa) may result in slower rate of diffusion of the botulinum toxin away from a site of intramuscular injection. Office Action of March 29, 2006 at pages 5-6.

As discussed above, Applicants have argued above that the claims are entitled to priority to the December 28, 1993 filing date of the '996 application. Given this priority date, the Han article (published 2001), the Kohl article (published in 2000), the Aoki patent (filed in 1999), and the Aoki publication (a divisional application having the same specification and same effective filing date ad the '996 application) are not prior art with regard to the pending claims. The Examiner has acknowledged that the obviousness rejection will be withdrawn upon granting of the priority date as the rejection contains

references which would not then be considered prior art with regard to the claims. Interview Summary of June 4, 2007 at page 3.

If, however, Applicants are not granted priority to the '996 application, Applicants assert that the claims are patentable over the combination of Balkan, Han, Kohl, Aoki, and Aoki for the reasons discussed below.

The Balkan and Han references relate to the injection of complexed botulinum toxin into a human muscle for treating strabismus. For reasons similar to those discussed above, there is no teaching or disclosure in the cited references, nor indeed any explicit rationale given by the Examiner, for why one of ordinary skill in the art would have modified the methods as disclosed in Balkan or Han in view of Kohl, Aokil, and Aoki to arrive at the presently claimed methods of administering a neurotoxic component to treat strabismus. Thus, the claims are not obvious over the Balkan or Han, Kohl, Aoki, and Aoki references, and a *prima facie* case of obviousness has not been established. Accordingly, the Board is requested to reverse the rejection of claims 1, 2, 4, 5, 29, 47, and 63 under 35 U.S.C. § 103(a).

Conclusion

Applicants respectfully request that the Board reverse the denial of priority of claims 1, 2, 4, 5, 29, 47, and 63 under 35 U.S.C. § 120 to parent application U.S. Serial No. 08/173,996 for lack of enablement, to reverse the rejections under 35 U.S.C. § 103(a) of claims 1, 2, 4, 5, 29, 47, and 63 over Balkan or Han in view of Tse, Kohl, and Aoki, and the rejections under 35 U.S.C. § 103(a) of claims 1, 2, 4, 5, 29, 47, and 63 over Balkan or Han in view of Kohl, Aoki, and Aoki.

Please charge the brief fee of $510 to Deposit Account No. 01-0885. Please apply any other charges or credits to Deposit Account No. 01-0885.

Respectfully submitted,

Date: July 2, 2008

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(8) Claims Appendix

1. A method for treating strabismus, the method comprising the step of administering to a patient a therapeutically effective amount of a neurotoxic component of a botulinum toxin to thereby treat strabismus wherein the neurotoxic component administered to the patient has a molecular weight of about 150 kilodaltons.

2. The method of claim 1, wherein the botulinum toxin is selected from the group consisting of botulinum toxin types A, B, C, D, E, F and G.

4. The method of claim 1, wherein the botulinum toxin is botulinum toxin type A.

5. A method for treating strabismus, the method comprising the step of administering to a patient a therapeutically effective amount of the neurotoxic component from only a botulinum toxin type A, to thereby treat strabismus, wherein the neurotoxic component administered to the patient has a molecular weight of about 150 kilodaltons.

29. A method for treating strabismus, the method comprising the step of administering to a patient a therapeutically effective amount of a neurotoxic component from a single botulinum toxin type selected from the group consisting of the botulinum toxin types A, B, C, D, E, F and G to thereby treat strabismus wherein the neurotoxic component administered to the patient has a molecular weight of about 150 kilodaltons.

47. The method of claim 5, wherein the neurotoxic component is administered by intramuscular injection.

63. The method of claim 29, wherein the neurotoxic component is administered by intramuscular injection.

(9) Evidence Appendix

Appendix	Document	Date Entered
A	Schantz *et al.*, *Microbiol. Rev.* 1992; 56(1):80-99	Response filed September 29, 2006
B	Wagman, J. *et al.*, *Arch Biochem Biophys* 1953; 45: 375-383	Response filed April 12, 2007
C	DasGupta, B., *et al.*, *J. Biol. Chem.* 1968 Mar 10; 243(5): 1065-1072	Response filed April 12, 2007
D	Schantz, E., pages 143-150 in Biomedical aspects of botulism, edited by Lewis, G., Academic Press, New York (1981)	Response filed April 12, 2007
E	Borodic, G. *et al.*, *Ophthalm Clinics of N. America* 1991 Sep; 4(3): 491-503	Response filed April 12, 2007
F	Declaration under 37 C.F.R. § 1.132 of Dr. Mitchell F. Brin	Response filed April 12, 2007
G	DasGupta, B.R., pages 15-39 in Therapy with Botulinum Toxin, edited by Jankovic, J. *et al.*, Marcel Dekker, Inc., New York (1994)	Response filed December 20, 2007
H	Tse, C.K. *et al.*, *Eur. J. Biochem.* 1982 ; 122 : 493-500	Cited by Examiner March 29, 2006
I	Lamanna, C., pages 333-335 in Botulinum and Tetanus Neurotoxins, edited by DasGupta, B., Plenum Press, New York (1993)	Response filed December 20, 2007
J	The Declaration under 37 C.F.R. § 1.132 of Dr. Leonard A. Smith	Response filed December 20, 2007
K	Lamanna C. *et al.*, *Arch. Int. Pharmacodyn. Therap.* 1988; 293: 69-83	Response filed December 20, 2007
L	Ph.D. thesis entitled *Characterization and stabilization of clostridium botulinum neurotoxin* by Michael C. Goodnough, published by the University of Wisconsin, March 10, 1994	Response filed December 20, 2007
M	Balkan *et al.*, *Annals of Ophthalmology* 1991; 23(9): 326-333	Cited by Examiner March 29, 2006
N	Han *et al. Journal of Pediatric Ophthalmology and Strabismus*, 2001; 38(2): 68-71	Cited by Examiner March 29, 2006
O	Kohl *et al.*, *Movement Disord.* 2000; 15(Suppl 3): 165	Cited by Examiner November 29, 2007
P	Aoki *et al.*, U.S. Patent No. 6,113,915	Cited by Examiner March 29, 2006
Q	Moyer, E. pages 71-85 in Therapy with Botulinum Toxin, edited by Jankovic, J. *et al.*, Marcel Dekker, Inc., New York (1994)	Response filed September 26, 2006
R	Aoki *et al.*, U.S. Publication No. 2001/0018415	Cited by Examiner March 29, 2006

(10) Related Proceedings Appendix

None.